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NUTRITION AND RESISTANCE TO INFECTION

By HOWARD A. SCHNEIDER, Ph.D., (Guest Editor)*

"A very great part of the mischiefs that vex this world arises from words."—EDMUND BURKE

Experimental nutrition is not very old. Despite this, the accomplishments in nutrition over a short span of roughly four decades are impressive. Since it is still a growing science, more successes are to be expected. One of these expectations is that the techniques of nutritional investigation can be brought to bear on some of the complex problems of infectious disease. This expectation reaches a simple formulation in the oft-used title of this review, "Nutrition and Resistance to Infection."

Is this formulation legitimate? Assuredly there is a body of concepts and techniques which we know as the science of nutrition; just as assuredly there is a whole array of phenomena which we know as infectious disease. But, is it proper to infer that there is any specific relationship between nutrition and infectious diseases? If there is a relationship is it fruitful, or even proper, to consider it in the framework conveyed by the word "resistance"? For that matter, what is "resistance"?

This may appear to be a negative way to approach the subject, but beginning with doubt is not always the worst way to start, and in fact it may well add to the credit of nutritional research that it has raised such questions and contributed some answers. The area of inter-penetration between two scientific disciplines is always one of interest but one which frequently presents problems of its own. So before proceeding to map this area it might be in order to pause for a telescopic view of the terrain into which we are advancing. This perspective might be gained by repeating here what was written on a similar occasion (1).

"By 'infection' we mean the process of interaction of two living entities, the infectious agent (bacterium, virus, protozoan, helminth, fungus, *etc.*) and the host.

"The observable effects of this interaction between host and infectious agent are termed 'infectious disease'. Several terms are commonly employed to describe the *degree* of this interaction. Thus, if the interaction does not occur, although the infectious agent has been presented to the host, the latter is described as 'resistant', or better, 'insusceptible'. Used in this way, the terms

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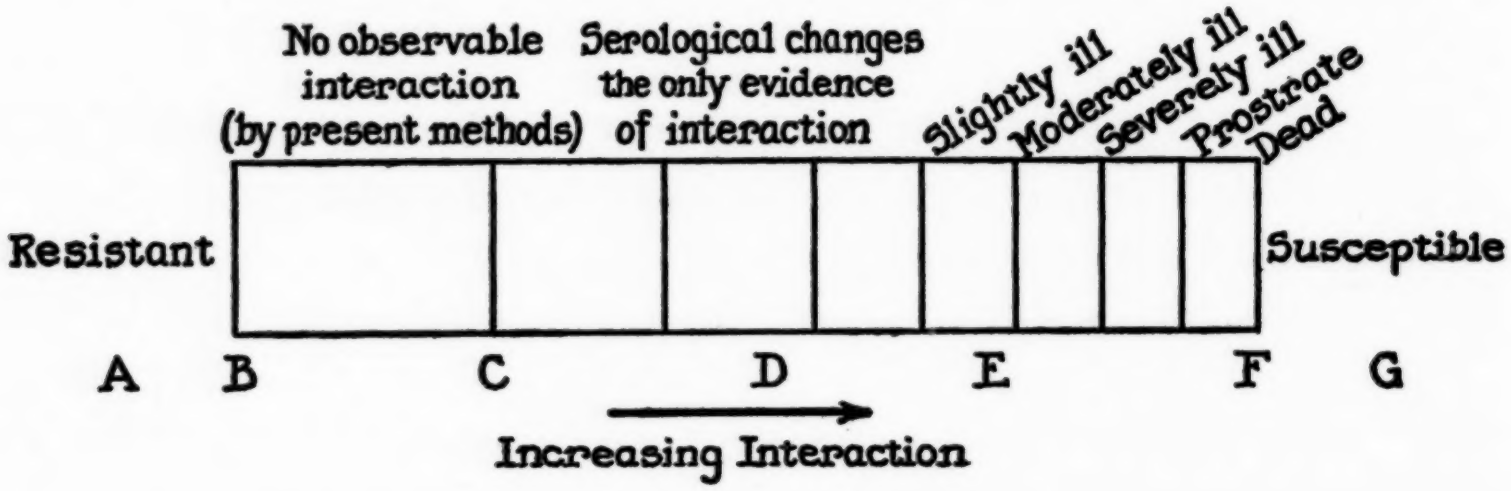
have an absolute meaning. In the same circumstances the infectious agent would be designated as 'avirulent'. When interaction does occur and is so extensive that the host dies, no one will quarrel with us if we then designate the host as 'susceptible' and the infectious agent as 'virulent'. When employed in this connection the words 'susceptible' and 'virulent' also have an absolute meaning. But very often, indeed most of the time, these terms will have a relative meaning, *i.e.,* hosts will be 'more resistant' or 'less resistant', and infectious agents will be 'more virulent' or 'less virulent'. The interaction of host and infectious agent is capable of producing a whole spectrum of phenomena which can be represented schematically as in Fig. 1.

FIGURE 1. The Spectrum of Host-Infectious Agent Interaction



"It is at once obvious that in attempting to apply the terms 'resistant' or 'susceptible' to a host, represented at 'D' in Fig. 1, a point of reference is necessary. Thus a host described at 'D' would be more resistant than hosts described at 'E', 'F', or 'G', but would be just as correctly termed as more susceptible than hosts described at 'C', 'B', or 'A'. When we speak of 'nutrition and resistance to infection', therefore, we really mean 'nutrition and resistance-susceptibility to infection'."

When the above was written in 1945 its service lay in its admission of the equal logic of considering susceptibility as well as resistance. It stripped the non-scientific anthropomorphism from the relation of nutrition to infection. From the standpoint of the potential host, man, "resistant" has happier connotations than "susceptible". Indeed, the field of infection is peculiarly loaded with anthropomorphisms, as witness such concepts as "the body's defenses", "war on disease", "the invasion of the pathogen", and others. The rejection of an anthropocentric view has now become more than a scientific nicety. The experimenters of modern nutritional research have made necessary a fresh, hard look at the concepts of "resistance" and "susceptibility". Thus, nutrition research is making an important theoretical con-

tribution to the whole field of infectious disease. What is this contribution and how is it affecting our perspective of the relation of nutrition to infectious disease?

The Separateness of Resistance and Susceptibility

In admitting resistance and susceptibility to an equal status as a matter of logic we are doing more than improving our technic as logicians. We are preparing our minds to anticipate that if nutrition can affect the phenomena of infectious disease it may well, like a two-edged sword, cut both ways.

In discussing the spectrum of infectious disease in the foregoing we were facing problems in *description.* For this purpose, resistance and susceptibility are relative terms applying to the same over-all phenomenon, infection. They merely point to different ends of the same scale of events as they occur in the infected host. In this view, for example, "more resistant" and "less susceptible" are equivalent, interchangeable, and of equal usefulness. Indeed, as long as we are content to use those terms in making *descriptive* statements in comparing one host with another we are in no particular difficulties. For simplicity let us say, following infection, Host A has survived and Host B has died. It matters little whether we say "Host A is less susceptible than Host B", or "Host A is more resistant than Host B". Either of these statements is effective. Both communicate the observation that Host A and Host B were subjected under suitably controlled conditions to a test infection and the outcome has led us to describe A as different from B. But although both statements describe the situation, they do not help us in *analyzing* it. In precisely what way did A differ from B? Did A's survival depend on a lesser susceptibility or a greater resistance? For if the only known difference between A and B was the diets they were eating, then we will want to know just what has been altered so that A survived and B died. As experimental nutritionists we need to know more about this matter. The methodology of our science is based in the last analysis, on a comparison between deficiency and abundance. Which diet, A's or B's, is the deficient diet? This is the semantic jungle in which we are tangled. How shall we find our way out? I believe the way out lies in regarding susceptibility and resistance as separate and distinct biological attributes, each capable of separate manipulation, be it enhancement or diminution. This, I think, has now become a necessity for purposes of unambiguous interpretation of results and the improved design of experiments. How did it happen that this problem has been raised by nutritional investigation and has not been particularly troublesome in previous ways of investigating infectious disease?

Interest in infectious disease has begun, rightfully, with the phenomenon of susceptibility, *i.e.,* the capacity of a host to entertain a microbic pathogen and respond to it with the symptoms and signs we label as disease. This must indeed be the beginning; without the phenomenon of susceptibility we would have no infectious disease. The study of the natural history of infectious disease in susceptible hosts soon revealed that (a) when a host recovered after an infectious disease experience it was somehow altered and (b) upon a subsequent exposure to the microbic pathogen oft-times proved to be refractory in the sense that disease was not made manifest during this second experience. This new state of affairs was shown to be not the exhaustion or substraction of the "something" in the host labeled "susceptibility". It was shown to be the addition to the host physiology of entities, *the antibodies,* which are the foundations of immunology. The change from a susceptible to a refractory state is the result of something which was added, rather than subtracted, which tended to oppose the original state of affairs. This new condition was more reasonably characterized by the use of a word which conveyed some notion of opposition to the original situation, i.e., such altered hosts had become "resistant". By and large, "susceptible" and "resistant" have served adequately to describe our verifiable observations of succumbing and surviving. Let me emphasize, however, that with usage, and dominated by the influence of the immunologist, survival of any kind has become a matter of "resistance". And resistance in turn has rested on notions that something has been added, or at least, enhanced. Here is the origin of the seemingly plausible view, that only *abundant* and *optimum* nutrition could fulfill this added requirement that resistance ostensibly poses. However, when we turn to the results of nutritional experimentation in the field of infectious disease we find that experience does not always fulfill this simple view. The hard fact is that increased survivorship, or diminished severity of disease, can be achieved by *withholding* certain items from the diet, and the same end can be reached by *adding* other items. Thus, the desired goal can be approached by diametrically opposed nutritional manipulations; deficiency on the one hand and supplementation on the other. The experimental basis for these statements will be examined in what follows, but it will be useful if we face up to this paradox here and now. If we are ever to make any sense of these data, I believe we must now regard susceptibility and resistance also as separate and distinct biological attributes of an animal in an absolute sense. Our confusion has arisen, I think, because these two opposed characters are simultaneously present in the host, and we are only aware of the resultant of these two opposed forces. Any given resultant — survival, death, or the stages between — can be achieved in two different ways: by the enhance-

ment of the one attribute, or the diminution of the other. The unambiguous operations of nutrition, the acts of withholding or supplying, now form a valid basis for deciding which of these alternative processes has taken place. We can now construct some operational definitions* which will unify what have appeared to be puzzling and contradictory experiences. When withholding a nutrient decreases the effect of an infection, and supplying the nutrient increases the effect, then we can say that the given nutrient is a susceptibility factor, and what we have affected is the character, "susceptibility". When experiment shows us that withholding a nutrient increases the effect of an infection, and supplying the nutrient decreases the effect, then we can say that the given nutrient is a resistance factor, and what we have affected is the character "resistance".

Using these operational definitions as touchstones we can now examine recent reports in the field of nutrition and infection and sort out answers to some of the questions we will want to ask.

Nutrition and Susceptibility

Can nutritional deficiency reduce the capacity of the host to respond to the pathogen? There are now some recorded instances in which this is the case.

Seeler and Ott (2) showed that riboflavin deficiency in chicks decreased the severity of *Plasmodium lophurae* infections. The administration of riboflavin to deficient birds during the course of the infection increased the severity of the infection.

McKee and Geiman (3) found that ascorbic acid deficiency in monkeys depressed the usual course of *Plasmodium knowlesi* infection, while supplementation with ascorbic acid resulted in increased parasitemia and death in 6—7 days.

In a virus disease of mice, mouse pneumonitis, Leftwich and Mirick (4) found that a short term deficiency of pyridoxine decreased the severity of the disease. Pyridoxine supplementation resulted in increased deaths.

In mouse salmonellosis Schneider (5) found that withholding fat from the diet resulted in increased survivorship, adding fat resulted in decreased survivorship.

Decreased deaths and paralysis in mouse infections with mouse-adapted poliomyelitis virus occurred in thiamine deficiency in experiments by Philadelphia (6) and Wisconsin (7) investigators. These two groups have con-

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*By appealing to operational definitions to clarify our concepts we are following Dr. P. W. Bridgman in his *"The Logic of Modern Physics,"* Macmillan Co., New York, 1927.

tinued their analysis of susceptibility to this viral disease with interesting results. Although protein deficiency reduced susceptibility only slightly, deficiencies of certain amino acids have had a convincing effect. Using a mixture of 16 amino acids as a source of nitrogen in the basal diet, several single amino acid deficiencies were studied for their effect on infection with the Lansing strain of mouse-adapted poliomyelitis virus (8). Those studied were valine, methionine, lysine, histidine, phenylalanine, leucine, threonine, isoleucine, and tryptophan. With the exception of lysine, all of the amino acid deficiencies studied affected the course of the viral disease. In the main these effects consisted of an increase in the length of time necessary for the symptoms of the disease to appear, a decrease in the number of animals paralyzed by the 28th day, and, interestingly, an increase in the number of animals which died without ever exhibiting the characteristic signs of the disease. The most effective deficiencies were those of tryptophan and isoleucine.

Here is an excellent example of the nutritional manipulation of susceptibility. Here, by unambiguous deficiency, susceptibility has been lowered. The reduction of the host's response to the pathogen is clearly indicated, for as these investigations have shown (8), the virus successfully multiplied in the brains of these deficient animals, and indeed in the instance of tryptophan deficiency, when virus levels in the non-deficient animals had declined, the tryptophan deficient tissues still showed high levels. Lack of disease was not for lack of virus.

From observations such as those above, it is evident that there is a growing segment of the literature on nutrition and infection which supports the thesis that nutritional deficiency is capable of reducing the effects of infections by reducing the host attribute of susceptibility. (For a brief discussion of susceptibility as an evolutionary character see Schneider (1)). This has now been shown for several hosts and for such diverse infections as those caused by protozoan, viral, and bacterial species. These effects have been elicited by deficiencies of amino acids, certain vitamins, fat, and even minerals (9).

The attention paid, since 1945, to the use of anti-metabolites suggests that susceptibility might be reduced by their use. Thus oxythiamine (10) and 6-methyl tryptophan (11) have been employed in the mouse-Lansing poliomyelitis model with results concordant with those obtained with the deficiencies produced in the usual way by omission of an amino acid. Whether this line of work will lead to therapeutically or prophylactically effective agents is an issue that only future research can decide. The threat to the health of the host, however, is not to be dismissed lightly and remains, for the time being, a real stumbling block to this strategic approach.

Nutrition and Resistance to Infection

Returning once again to an operational definition it will be recalled that a given nutrient was logically identified as a resistance factor when deficiency increased the effect of the infection and supplying the nutrient decreased the effect of the infection. This is simple enough, and what most of us had in mind, probably, when we first turned our thoughts to this subject. But before we can proceed we must reckon with a new fact. For although there is only a single notion involved in the concept of susceptibility, resistance to infection may be of several kinds. What these kinds are can be summarized in Table 1.

TABLE 1.

Several Kinds of Resistance to Infection*

I. Innate resistance ("natural resistance").
Genetic basis; between or within species.

II. Acquired resistance (immunity).

A. Active. (The host participates in the formation of immune bodies.)

1. Naturally acquired. (By sublethal experience with the infectious agent.)

2. Artificially induced. (By injection of an immunologically active form of the infectious, or specifically related, agent.)

B. Passive. (The immediate host does not participate in the formation of immune bodies.)

1. Naturally acquired (congenital).

2. Artificially induced. (By injection of immune bodies produced in another host.)

Because there are several distinct kinds of "resistance," each with its own distinct operational basis, it is evident that for purposes of precision one must specify the particular kind of "resistance" under consideration. This will enable us to sort into some kind of order the voluminous literature concerned with these matters. (Bibliographic entry into this literature can be gained

*Immunologists have recently added still another kind of acquired active resistance which has its biological basis in the "interference phenomenon." Resistance here follows prior infection with an immunologically unrelated infectious agent having a cellular predilection similar to that of the test infecting agent. The phenomenon is of short duration and any relationship of nutrition to it remains completely unexplored.

from the following reviews: S. W. Clausen (12), E. C. Robertson (13), W. L. Aycock and G. E. Lutman (14), H. A. Schneider (1, 15), P. F. Clark *et al.* (16), P. Cannon (17), J. W. Howie (18)).

Nutrition and Innate Resistance (Natural Resistance)

Since the great bulk of the literature of nutrition and resistance is devoted to *natural* resistance, and is as confused as it is devoted, it perhaps would be well if we are as clear as possible as to what is concerned here.

When we use the term "natural resistance" we take cognizance of those differences among potential hosts, which, without previous experience of the pathogen, result in diverse response upon initial contact with the pathogen. When we categorize these differences in response we find that, following the taxonomist, there are susceptible species and "naturally resistant" species. Again we find that as a descriptive statement this is perfectly adequate, but in an analytic sense the doubt can be raised as to whether these "naturally resistant" species are more correctly regarded as "non-susceptible" species, in the sense that they actually lack the biochemical basis of susceptibility. Unfortunately, at the species level, there are no data to allow us to decide this matter. We must, for the time being, be content with the descriptive statement. We are somewhat better off when we next inquire as to differences in natural resistance *within* a responding, or to some degree, susceptible, species. Ever since Webster's classical work (19) reported in 1937 on the genetics of resistance of mice to salmonellosis, there has been assurance that intraspecific natural resistance was a real and manipulable biological entity. Webster (19) also showed that resistance to one disease and the lack of resistance to another could be assembled into the same animal. This demonstration effectively demolishes any notions of a "pan-resistance," a biological fact which should be remembered in any discussion of natural resistance. We must now face up to the question whether nutrition is similarly capable of manipulating intraspecific natural resistance such as has been achieved by breeding experiments. This mention of genetics should make us wary, and we now must rephrase our question to inquire: under what genetic circumstances can nutrition influence survivorship following infection?

The role of the genotypic constitution of host and pathogen populations in the design of nutritional experiments in natural resistance has been a concern of the writer. These investigations (20) employing a mouse-salmonellosis model have led to a general formulation such as is presented in Fig. 2.

From this scheme it follows that a nutrition experiment on natural resistance is made up of a suitably *genetically heterogenous host* and infection is performed with a *heterogenous pathogen population.* Here is the area in

FIGURE 2.*

The Effect of a Natural (N) and a Synthetic (S) Diet on Survivorship following Infection in Nine Different Genetic Circumstances

		Host-Genotype		
		Inbred, selected, resistant	Random-bred, (outbred) non-selected	Inbred, selected, susceptible
Pathogen-Genotype	Uniformly virulent	N-Died S-Died	N-Died S-Died	N-Died S-Died
	Mixed virulent and avirulent	N-Survived S-Survived	N-Survived ↑ Dietary effect ↓ S - Died	N-Died S-Died
	Uniformly avirulent	N-Survived S-Survived	N-Survived S-Survived	N-Survived S-Survived

which nutrition can work. In many ways it is closer to the natural world than the usual type of experiment heretofore designed. It need hardly be pointed out that human populations are genetically heterogeneous. The same is probably true for pathogen populations. Future exploitation of infection models of this type would seem to be a worthwhile undertaking. It is at this point that nutrition has made a theoretical contribution to the study of infectious disease. Let us examine Fig. 2 more closely. It shows that the nutritional manipulation of survivorship in this infection is dependent upon an array of variations in the pathogen population. It shows also that hosts in which surviving or succumbing has been arranged by genetic means, independent of diet, respond in this way only when again the pathogen population is composed of an array of variants. Indeed, if, as Fig. 2 shows, we infect so-called

*From H. A. Schneider, in "Biological Foundations of Health Education." Columbia University Press, New York, 1950.

genetically resistant animals with a uniform, virulent bacterial population, such animals do not survive. Where then is their resistance? The prime message of Fig. 2 is that natural resistance, although an attribute of the host, has its expression inextricably linked with the nature of what we might call the structure of the pathogen population. The fundamental problem at the root of natural resistance is therefore a problem involving pathogens as heterogenous populations. Intraspecific natural resistance, then, is the successful solution of what is probably a metabolic problem which is precipitated by certain members of the pathogen population, and which is solved by the presence, and probable action of other members of the pathogen population. Natural resistance, though it is an attribute of the host, is not to be conceived as a barrier, an antibiotic, or opposed force. It should be considered a positive entity, biochemical in nature, which arranges for survivorship by assisting certain members of the pathogen population to come into adjustment with other members, and thereby permits a silent coexistence of pathogen and host in which both survive as representatives of their species. This notion of natural resistance conceived as a pathogen intra-populational problem has many interesting consequences, not the least of which is the possibility of abstracting the crucial intra-populational problem from the host into the test tube. By pointing to the importance of the frequency distribution of the numerous variants in the pathogen population we can understand the general plasticity of such pathogenic agents as viruses upon their original isolation from nature and the consequences of laboratory passage through uniform hosts upon their more uniform behavior and increased "suitability" as items for study. What would it mean, for example, to use heterogeneous, unselected virus populations for nutritional experiment? And what are the consequences of attempting the same study with virus populations, after many laboratory passages, and of "uniform titer"? Similar questions suggest themselves whenever we reflect on the population structure of the pathogen used in our experiments, be they protozoan, viral, fungal or bacterial.

Let us sum up, then, this contribution to the study of infectious disease. Intraspecific natural resistance was shown to be influenced by nutrition only when the host was genetically heterogeneous and the pathogen population was heterogeneous in the sense that it contained an array of variation in terms of capacity to produce disease. When the pathogen population was uniform, host difference, genetic or nutritional, had no effect. The outcome was decided by the nature of the uniform pathogen population. In a word, natural resistance disappeared. From this we can construct an operational definition of intraspecific natural resistance. The phenomenon has its basis in the host, but the solution of the situation has *its* basis in the intra-populational prob-

lem of the pathogen. Thus the host and the pathogen population are inextricably woven into the conceptual fabric we know as intraspecific natural resistance.

From a nutritional viewpoint some interest has attached to the mouse-salmonellosis investigations summarized above because the dietary resistance factor has been shown to be a new nutritional entity found in a variety of sources such as wheat, corn, alfalfa, yeast. In wheat it is concentrated in the germ and can be extracted by acid alcohol (21). Its chemical nature remains unidentified.

The literature records instances in which known nutritional factors have been able to influence infection in a manner which fulfills our operational definition for a resistance factor, although the genotypic structure of the host and pathogen populations were not analyzed. Thus Trager (22) found biotin deficiency to exacerbate *Plasmodium lophurae* infection in both chicks and ducks. Seeler and Ott (23) found a similar effect in folic acid deficiency. In prolonged pyridoxine deficiency in mice, Mirick and Leftwich (24) found the response to pneumonitis virus to be enhanced. Caldwell and György (25) found that the effects of *Trypanosoma lewisi* infection in rats were increased by biotin deficiency in proportion to the deficiency. Excess biotin administered to normal rats had no protective or curative effects on infections with *T. lewisi.* Roos, Hegsted and Stare (26) have reported that nicotinic acid deficiency in chicks resulted in severer infection with *Plasmodium lophurae.* Thiamine deficiency was without effect and vitamin A deficiency led to a lessening of the effects of the infection (reduction in susceptibility!).

Further extension of this list may be made by consulting the reviews mentioned above. Extending the list, however, will not necessarily add to its meaning. What confronts us here is the problem of extracting what sense we can, in order to integrate our outlook on these phenomena. It will be helpful if we return to our point of departure. There we were led to recognize that resistance and susceptibility were separable biological attributes of the host. Those nutrient entities for which absolute requirements are known for growth and support of life processes in general might be expected to be rather non-specific in their support of these two attributes. The effect of dietary deficiency might well be diminishing both of these attributes, just as total body weight is limited, but since the resultant of the two opposite tendencies would thus remain unchanged, we might remain in ignorance of such effects. The necessity of providing for severe deficiencies in classical nutrition studies suggests that those nutrients which have come to our attention as the result of such work are perhaps rather remotely and non-specifically con-

cerned with both resistance and susceptibility. It may be that we need to return to the world of natural foodstuffs to inquire whether they contain still unknown factors which more intimately and selectively are concerned with each of these separate attributes. *What is certain is that no single nutrient now known has emerged as being uniquely involved in the problems of either susceptibility or resistance.* When any given nutrient has been shown to have one effect on natural resistance in one infectious disease it may have the opposite effect in a second infectious disease, and in *n* infectious diseases it may have no effect whatever.

Nutrition and Acquired Resistance

The relation of nutrition to *passively* acquired immunity, either natural or artificially induced, is a little-touched area in modern experimentation. This is probably due to the relative lack of interest in the phenomenon of passive immunity compared to that focussed on actively acquired immunity in the attempt to devise immunologic means to cope with some of the still-unconquered infectious diseases, especially in the group of viral diseases.

In the past few years there has been a fresh burst of activity in examination of the role of nutrition in relation to *actively* acquired immunity, especially that achieved by artificial induction. Anyone reading recent publications in this field is struck at once by the absence of the semantic problems and confusion which has so beset the field of natural resistance. There is probably a good reason for this. The term implies man-invented, artificially induced active immunity. The absence of semantic problems does not mean that there is complete agreement about the significance of the results obtained. At the present, however, certain developments can be appraised.

When the immunologist induces an artificially acquired immunity he brings into effective contact with the host, usually by injection, an immunologically active form of the infectious agent. This latter might be a vaccine, living or killed, or a chemically prepared fraction of the infectious agent or a closely related form. Thus introduced, in one way or another, the important event is that the material introduced is antigenic and elicits from the host the formation of specific proteins called the antibodies. These antibodies form the physical basis of the refractory state of the host called immunity. Since the host participates in the formation of the antibodies it is logical to inquire whether its nutritional state can influence this formation. This is the point at which nutrition arrives in the design of inquiry. Now, since the antibodies are proteins it follows that host protein intake should be looked into. This has been done.

Proteins and Antibody Formation

The modern analysis of this problem has been largely conducted by P. Cannon and his school. This group has shown (17) that in the rabbit and rat a prolonged inadequacy of protein intake severe enough to cause a marked depletion of protein reserves lessens the capacity of the antibody-producing tissues to synthesize a spectific antibody. The antibodies measured have been of several kinds including agglutinins, precipitins and hemolysins. In examining experiments of this kind one is struck by the need of prolonged and severe protein deficiency to produce important differences in the antibody titers observed. In some of their experiments, the Cannon school has resorted to plasmapheresis to achieve results. Apparently the capacity to fabricate antibodies is conserved to the last possible moment in the face of protein depletion. In human beings this would seem to be true as well. Thus Gell (27), in reporting some experiments on antibody formation capacity performed in Germany in 1946, under the aegis of the Medical Research Council, on members of the population exhibiting extreme inanition, has this to say on the differences observed:

"I would draw attention to three points: (1) The extremely severe degree of undernutrition from which the test subjects were suffering—severe enough to render active life impossible; and (2) in spite of this, the comparatively small differences between these literally famished subjects and the controls, in first-class condition; (3) the significant fact that there actually has not been any widespread epidemic disease in Germany since the end of the war."

Vitamins and Antibody Formation

The problem of the generation of antibodies involves not only their material substance, the amino acids, but also the dynamics and energetics of their formation as specific configurations of gamma globulins. Apart from the former, which has been considered above, there has been a recent trend to examine the role of vitamins proceeding from theoretical considerations suggested by the latter. This role of the vitamins has recently been reviewed by Axelrod (28). Work in this area received its original impetus from the work of H. C. Stoerk and his collaborators (29). These workers demonstrated a striking impairment of the antibody response to sheep erythrocytes in pyridoxine deficient rats. This has been confirmed by Axelrod and coworkers (30). They used human erythrocytes as the antigenic stimulus and observed an equally impaired antibody production in pantothenic acid deficiency and a moderate inhibition in riboflavin deficiency. Axelrod has now classified the effects of vitamin deficiency on the hemagglutinin response

of the rat to the antigenic stimulus of human erythrocytes as follows: Group I; severe impairment of antibody response, pantothenic acid, pyridoxine and pteroylglutamic acid deficiencies. Group II; moderate impairment of antibody response, riboflavin, thiamine, biotin, vitamin A and niacin-tryptophane deficiencies. Group III; no impairment of antibody response, vitamin B_{12} and vitamin D deficiencies. From the work published it is evident that these effects are not attributable to inanition.

It must be borne in mind in considering the interesting results sketched above that the antigenic stimulus has been the erythrocyte and not an infectious agent. This is not to deny the suggestive nature of this kind of investigation, but surely work with antigens derived from infectious agents will be needed before we will be able to advance from this outpost into the arena of nutrition and infection.

Summary

In leaving this interesting and somewhat confused subject of nutrition and infection what can be concluded? It can be said that at present there is no known nutrient, or component of human diets, which, compared with vaccination or known chemotherapeutic agents, can compellingly interest the student of public health as a practical measure in the control of infectious disease. Modern nutritional research, however, is now coming into effective contact with the problems of infectious disease and its contributions at the level of theory are fresh, novel, and important. It has compelled a fresh examination of the concepts of resistance and susceptibility and has provided evidence for considering these as separate and manipulable biological attributes. Nutritional research has clarified some puzzling aspects of natural resistance and has demonstrated the important role of genetic heterogeneity in the pathogen population as the seat of the events which lead to survivorship in an infectious disease. It has pointed the way to the identification of some new nutritional factors involved in these affairs. And lastly, it has opened some new approaches to the problems of antibody formation. It is the consequences of these contributions to the theory of infectious disease which lie in the future ahead of us.

REFERENCES CITED

1. SCHNEIDER, H. A. Nutrition and Resistance to Infection — the Strategic Situation. *Vitamins and Hormones, 4:* 35–70 (1946).

2. SEELER, A. O., and Ott, W. H. Effect of riboflavin deficiency on the course of *Plasmodium* infection in chicks. *J. Infect. Dis., 75:* 175 (1944).

3. MCKEE, R. W., and Geimann, Q. M. Studies on malarial parasites. V. Effects of ascorbic acid on malaria *(Plasmodium knowlesi)* in monkeys. *Proc. Soc. Exp. Biol. Med. 63:* 313 (1946).

4. LEFTWICH, W. B., and Mirick, G. S. The effect of diet on the susceptibility of the mouse to pneumonia virus of mice (PVM). I. Influence of pyridoxine in the period after the innoculation of virus. *J. Exp. Med., 89:* 155 (1949).

5. SCHNEIDER, H. A. Unpublished experiments.

6. FOSTER, C., Jones, J. H., Henle, W., and Dorfman, F. The comparative effects of vitamin B_1 deficiency and restriction of food intake on the response of mice to the Lansing strain of poliomyelitis virus, as determined by the paired feeding technique. *J. Exp. Med., 80:* 257 (1944).

7. RASMUSSEN, A. F., JR., Waisman, H. A., Elvehjem, C. A., and Clark, P. F. Influence of the level of thiamine intake on the susceptibility of mice to poliomyelitis virus. *J. Infect. Dis., 74:* 41 (1944).

8. DAVIES, W. L., Pond, W. L., Smith, A. F., Rasmussen, A. F., Jr., Elvehjem, C. A., and Clark, P. F. The effect of certain amino acid deficiencies on Lansing poliomyelitis in mice. *J. Bact., 64:* 571 (1952).

9. LICHSTEIN, H. C., McCall, K. B., Plass, B. A., Maddy, K. H., Elvehjem, C. A., and Clark, P. F. Effect of minerals on susceptibility of Swiss mice to Theiler's virus. *Proc. Soc. Exp. Biol. Med., 62:* 279 (1946).

10. JONES, J. H., Foster, C., and Henle, W. Effect of oxythiamine on infection of mice with the Lansing strain of poliomyelitis virus. *Proc. Soc. Exp. Biol. Med., 69:* 454 (1948).

11. RASMUSSEN, A. F., JR., Clark, P. F., Smith, S. C., and Elvehjem, C. A. Effect of 6-methyl tryptophan on Lansing poliomyelitis virus in mice. *Bact. Proc.,* 1951, 93.

12. CLAUSEN, S. W. The influence of nutrition upon resistance to infection. *Physiol. Rev., 14:* 309 (1934).

13. ROBERTSON, E. C. The vitamins and resistance to infection. *Medicine, 13:* 123 (1934).

14. AYCOCK, W. L., and Lutman, G. E. Vitamin deficiency as an epidemiologic principle. *Am. J. Med. Sci., 208:* 389 (1944).

15. SCHNEIDER, H. A. Nutrition and resistance — susceptibility to infection. *Am. J. Trop. Med., 31:* 174 (1951).

16. CLARK, P. F., McClung, L. S., Pinkerton, H., Price, W. H., Schneider, H. A., and Trager, W. Influence of nutrition in experimental infection. *Bact. Rev., 13:* 99 (1949).

17. CANNON, P. The relationship of protein metabolism to antibody production and resistance to infection. *Advances in Protein Chemistry, 2:* 135 (1945).

18. HOWIE, J. W. Nutrition and susceptibility to infection. *Brit. J. Nutr., 2:* 331 (1949).

19. WEBSTER, L. T. Inheritance of resistance of mice to enteric bacterial and neurotropic virus infections. *J. Exp. Med., 65:* 261 (1937).

20. SCHNEIDER, H. A. Nutrition of the host and natural resistance to infection. IV. The capability of the double strain inoculation test to reveal genetically determined differences in natural resistance to infection. *J. Exp. Med., 89:* 529 (1949). Also preceding papers in this series.

21. SCHNEIDER, H. A. Relation of a specific nutrient in wheat to natural resistance to infection. *Trans. Am. Assoc. Cereal Chem., 7:* 4 (1949).

22. TRAGER, W. The influence of biotin upon susceptibility to malaria. *J. Exp. Med., 77:* 557 (1943).

23. SEELER, A. O., and Ott, W. H. Effect of deficiencies in vitamins and protein on avian malaria. *J. Nat. Malaria Soc., 5:* 123 (1946).

24. MIRICK, G. S., and Leftwich, W. B. The effect of diet on the susceptibility of the mouse to pneumonia virus of mice (PVM). II. Influence of pyridoxine administered in the period before as well as after the inoculation of virus. *J. Exp. Med., 89:* 175 (1949).

25. CALDWELL, F. E., and György, P. The influence of biotin deficiency on the course of infection with *Trypanosoma lewisi* in the albino rat. *J. Infect. Dis., 81:* 197 (1947).

26. ROOS, A., Hegsted, D. M., Stare, F. J. Nutritional studies with the duck. IV. The effect of vitamin deficiencies on the course of *P. Lophurae* infection in the duck and the chick. *J. Nutr., 32:* 473 (1946).

27. GELL, P. G. H. Discussion on nutrition and resistance to infection. *Proc. Roy. Soc. Med., 41:* 323 (1948).

28. AXELROD, A. E. Vitamins and antibodies. *Nutr. Rev., 10:* 353 (1952).

29. STOERK, H. C., Eisen, H. N., and John, H. M. Impairment of antibody response in pyridoxine-deficient rats. *J. Exp. Med., 85:* 365 (1947).

30. LUDOVICI, P. P., and Axelrod, A. E. Circulating antibodies in vitamin-deficiency states. Pteroylglutamic acid, niacin-tryptophan, vitamins B_{12}, A, and D deficiencies. *Proc. Soc. Exp. Biol. Med., 77:* 526 (1951). And preceding papers.

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We welcome him as a contributor to *Borden's Review of Nutrition Research* and wish him success in his future work.

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